wherein said first microparticles are coated with a first binding partner reactive to an analyte, and second microparticles of 30-600 nm in diameter having a refractive index wherein said second microparticles are coated with a second binding partner reactive for said analyte and said first microparticles have stronger light scattering properties than said second microparticles, and said first binding partner coated upon said first microparticles has a higher reactivity for said analyte than said second binding partner coated upon said second microparticles.

REMARKS

Claims 1- 17 and 19-21 remain active in this application. Reconsideration is respectfully requested. Applicants' specification is amended at page 1, line to indicate that parent application Serial No. 09/827,546 has issued as U.S. Patent No. 6,248,597, on June 19, 2001.

In an effort to expedite the prosecution of the above-identified patent application, Claim 18 is canceled as it is believed to be redundant and Claim 21 amended to recite that the reagent prepared by the claimed method is a reagent for an agglutination assay, thus aligning the scope thereof with Claim 1 and the teachings of Applicants' specification.

The rejection of Claim 21 under the second paragraph of 35 U.S.C. §112 is respectfully traversed. The Examiner asserts that it is necessary for the claim to recite a difference in particle size between 30-600 nm. Applicants respectfully disagree. It is taught in the instant specification at page 8, beginning at line 10, that the particles of the reagents of the invention differ in light scattering properties due a difference in particle size, refractive index or both. It is further taught on page 9, lines 1 to 3 that the size ratio of larger to smaller particles is from about 1.5 to 4. It is respectfully submitted one of ordinary skill in the art, given the teachings in Applicants' specification that the difference in size between two groups of particles or the difference in refractive index of material of two groups of particles of the same size will yield the desired difference in light scattering properties, can readily appreciate and reproduce the limitations of Claim 21. The recited range represents no more than a minimum and maximum particle size for the claimed compositions and is definite within the meaning of the second paragraph of 35 U.S.C. §112 without further amendment. Accordingly, withdrawal of the rejection is in order and is respectfully requested.

The rejection of Claims 1-8, 10-12 and 21 under 35 U.S.C. §103(a) as being unpatentable over Grange *et al.* in view of Lindmo *et al.* is respectfully traversed. Grange *et al.*, as correctly noted in the Office Action under reply, teach agglutination assays in which antigens and antibodies are covalently bound to light scattering particles and analyte concentration is measured by nephelometry. Regardless of the other general similarities between the overall teaching of Grange *et al.* and Applicants' invention noted in the Office Action under reply, there is a fundamental difference and distinction between them that is also correctly pointed out in the Office Action under reply. Grange *et al.* fails to anticipate Applicants' invention as defined by the claims under consideration or render it unpatentable because it fails to teach differential characterization between microparticles of specific size populations, differential reactivity and dissociation constants between two immunological binding partners. Since the teachings of Grange *et al.* fail to suggest the diagnostic methodology of Applicants' invention, it is respectfully submitted that no motivation can be drawn therefrom for one of ordinary skill in the art to prepare the reagents as claimed in Claims 1-17 and 19 and 20, or to prepare such a reagent by the method of Claim 21.

In implicit recognition of the deficiency in the teachings of Grange *et al.*, Lindmo *et al.* is combined therewith in making the rejection. It is respectfully submitted, however, that the two are not properly combinable. Lindmo *et al.* teach an assay based on flow cytometry, which is based on totally different principles than microparticle-enhanced light scattering agglutination assays. In assays by flow cytometry, there is no aggregation of microparticles and the amount of soluble labeled antibody is determined for each particle individually as they are separated and, possibly, also by distinguishing characteristics if such exist and are detectable by the flow cytometer. Because Grange *et al.* and Lindmo *et al.* teach assays that are based on clearly distinct principles, it is respectfully submitted that there would be no motivation for one of ordinary skill in the art to combine them to create the novel reagents of the Claims under consideration. Further, since the assay taught by Lindmo *et al.* does not involve agglutination, there would be no teaching therein from which one of ordinary skill in the art would be motivated to create any reagent for an assay involving agglutination. Withdrawal of the rejection is clearly in order and is respectfully requested.

The rejection of Claim 9 under 35 U.S.C. §103(a) as being unpatentable over Grange *et al.* in view of Lindmo *et al.*, further in view of Sutton *et al.* is respectfully traversed. Grange *et al.* and Lindmo *et al.* have been discussed above. It has been established that one of ordinary skill in the art would not be led to create the reagents of the Claims under consideration by combining their teachings because the assays they describe are based on different principles. Sutton *et al.* teaches specific copolymers coated on the surface of insoluble particles and having covalently bound thereto an oligonucleotide complimentary to a nucleic acid analyte. Such a teaching is respectfully submitted to be unrelated to the assay taught by Lindmo *et al.* and does not render Claim 9 unpatentable in combination with Grange *et al.* since it does not cure the deficiencies of Grange *et al.* as it applies to Claim 1. Therefore, based only on the fact that Sutton *et al.* teaches the use of oligonucleotide capture probes for a nucleic acid analyte, which is known in the art, it is respectfully submitted that one of ordinary skill in the art would not be led to create the reagent of Claim 9 by combining the teachings of Sutton *et al.* with Grange *et al.* and certainly not by combining the teachings of Sutton *et al.* with either Lindmo *et al.* or Lindmo *et al.* and Grange *et al.* since their teachings are not combinable as pointed out above. Withdrawal of the rejection is respectfully requested.

The rejection of Claims 13-17, 19 and 20 under 35 U.S.C. §103(a) as being unpatentable over Grange *et al.* in view of Lindmo *et al.* further in view of Harchali *et al.* is respectfully traversed. Grange *et al.* and Lindmo *et al.*, and their respective shortcomings, have been discussed above. It has been established that one of ordinary skill in the art would not be led to create the reagents of the Claims under consideration by combining their teachings because they operate on different principles. Harchali *et al.* is cited as a teaching of polyacrylic, polyfunctional, copolymerized microparticles conjugated with antigens of defined epitopic specificity, used "in an agglutination essay". The assay of the citation, in distinct contrast to that of the claims under consideration, is based on the absence of agglutination. Hence, one of ordinary skill in the art seeking new reagents useful in agglutination reactions would not look to the teachings of Harchali *et al.* and would certainly have no motivation to combine their teachings with either Grange *et al.* or Lindmo *et al.*, particularly the latter. Withdrawal of the rejection is in order and is respectfully requested.

Accordingly, it is respectfully submitted that, as Claims 1-17 and 19-21 meet the requirements of the second paragraph of 35 U.S.C. §112 and clearly define patentable subject matter over the citations cited of record, this application is in condition for allowance. An early Notice of Allowance is courteously solicited.

In the event the Examiner deems a further discussion of this application would expedite prosecution to allowance, the undersigned Attorney of Record would welcome the opportunity to hold such a discussion. The Examiner's cooperation in this regard is sincerely appreciated

Respectfully submitted,

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AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

21. (Amended) A method of preparing a microparticle reagent **for an agglutination assay** which comprises mixing first microparticles of 30-600 nm in diameter having a refractive index wherein said first microparticles are coated with a first binding partner reactive to an analyte, and second microparticles of 30-600 nm in diameter having a refractive index wherein said second microparticles are coated with a second binding partner reactive for said analyte and said first microparticles have stronger light scattering properties than said second microparticles, and said first binding partner coated upon said first microparticles has a higher reactivity for said analyte than said second binding partner coated upon said second microparticles.